

**PARTICLES COMPRISING AMPHIPHILIC COPOLYMERS, HAVING A CROSS-LINKED SHELL DOMAIN AND AN INTERIOR CORE DOMAIN, USEFUL FOR PHARMACEUTICAL AND OTHER APPLICATIONS****Publication number:** JP2001508762 (T)**Publication date:** 2001-07-03**Inventor(s):****Applicant(s):****Classification:**

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A61P43/00; C08F293/00; C08J3/24; C08L101/00;  
C08L53/00; C12N11/08; A01N25/26; A61K31/74; A61K9/51;  
A61K9/52; A61P3/00; A61P43/00; C08F293/00; C08J3/24;  
C08L101/00; C08L53/00; C12N11/00; (IPC1-7): A61K9/52

- European: A61K9/51; C08J3/24H

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WO9749736 (A2)

WO9749736 (A3)

WO9749387 (A1)

JP2000514791 (T)

EP0907666 (A1)

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Abstract not available for JP 2001508762 (T)

Abstract of corresponding document: **WO 9749736 (A2)**

Provided are methods of inhibiting bile acid uptake from the gastrointestinal system and reducing blood serum cholesterol by administering to a mammal, such as a human, an effective amount of particles comprising amphiphilic copolymers, having a cross-linked shell domain and an interior core domain.

Data supplied from the **espacenet** database — Worldwide

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A 61 K 9/52

識別記号

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A 61 K 9/52

審査請求 未請求 予備審査請求 有 (全175頁)

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(31)優先権主張番号 60/020,693  
(32)優先日 平成8年6月27日(1996.6.27)  
(33)優先権主張国 米国(US)

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最終頁に続く

(54)【発明の名称】 架橋した外殻領域および内部芯領域を有する両親媒性コポリマーからなり、医薬およびその他の用途に有用な粒子

(57)【要約】 架橋シェルドメインと内部コアドメインを有する両親媒性コポリマーを含む粒子が提供される。また、このような粒子を含む組成物(薬剤組成物を含む)、この粒子の製造方法、および例えば薬剤活性のある物質の送達のためのこのような粒子の使用方法も提供される。

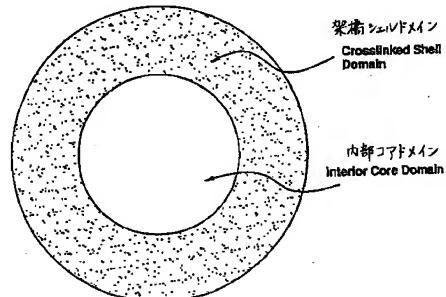


FIG.1









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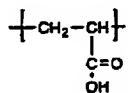




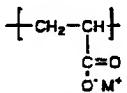
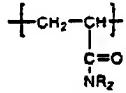
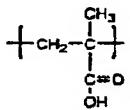
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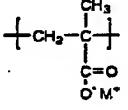
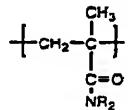
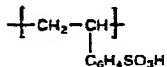
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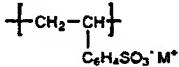
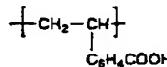
ポリアクリル酸

ポリ(金属アクリレート)  
 $\text{M = Li, Na, K, Cs}$ ポリアクリルアミド  
 $\text{R = H, アルキル}$ 

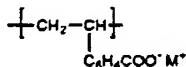
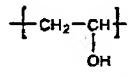
ポリ(メタアクリル酸)

ポリ(金属メタアクリレート)  
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 $\text{R = H, アルキル}$ 

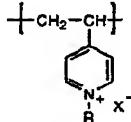
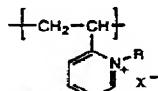
ポリスチレンスルホン酸

ポリスチレンスルホン酸, 金属塩  
 $\text{M = Li, Na, K, Cs}$ 

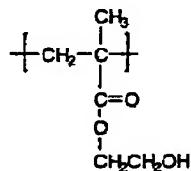
ポリスチレンカルボン酸

ポリスチレンカルボン酸, 金属塩  
 $\text{M = Li, Na, K, Cs}$ 

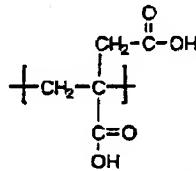
ポリ(ビニルアルコール)

 $\text{R = H, アルキル}$  $\text{R = H, アルキル}$ ポリ(2-ビニル-N-アルキル  
ピリジニウム ハライド)ポリ(4-ビニル-N-アルキル  
ピリジニウム ハライド)

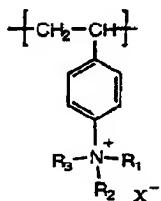
四級化パーセント 10% ~ 70%



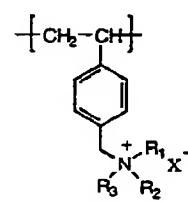
ポリ(ヒドロキシエチルメタクリレート)



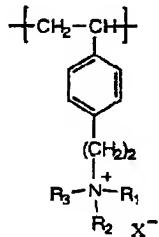
ポリ(イタコン酸)



ポリ(N,N,N-トリアルキル-4-  
ビニルフェニルアンモニウム ハライド)



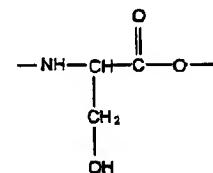
ポリ(N,N,N-トリアルキル-4-  
ビニルベンジルアンモニウム ハライド)



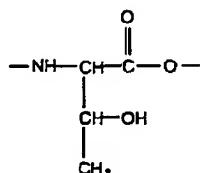
ポリ(N,N,N-トリアルキル-4-  
ビニルフェネチルアンモニウム ハライド)

四級化パーセント 10% ~ 70%

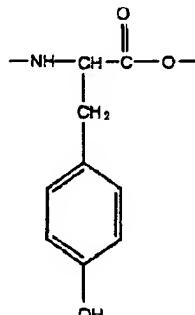
親水性ブロックを構成するアミノ酸



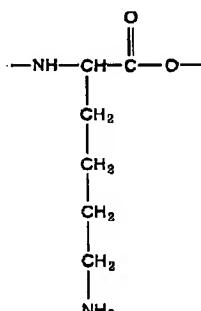
セリン



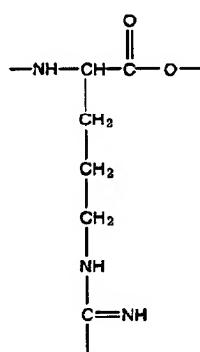
スレオニン



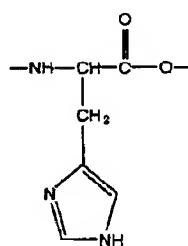
チロシン



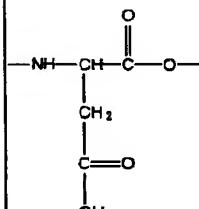
リジン



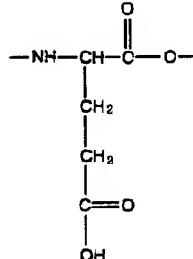
アルギニン



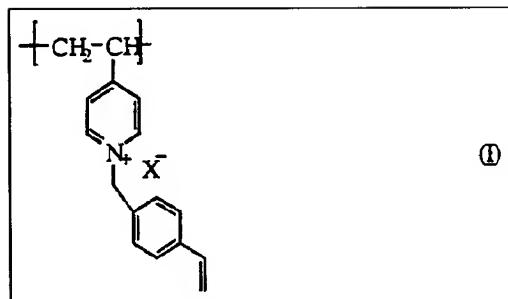
ヒスチジン



アスパラギン酸



グルタミン酸













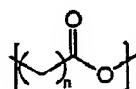
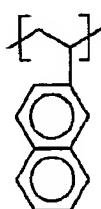




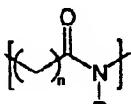


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疎水性反復単位



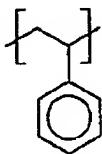
ポリ(カプロラクタム)



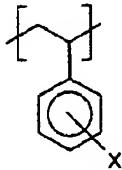
$R = H, CH_3$ , アルキルまたは  
アリール基

ポリ(アミド)

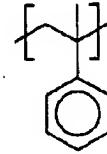
ポリ(2-ビニルナフタレン)



ポリスチレン

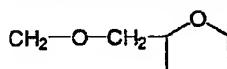


ポリ(p-X-スチレン)

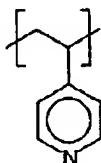


ポリ(α-メチルスチレン)

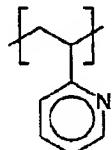
$X = \text{アルキル}, CH_3, t\text{-}Bu, OCH_3, CH_2Cl, Cl, CN, CHO$



, アルケニル, アルキニル

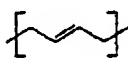


ポリ(4-ビニルピリジン)



ポリ(2-ビニルピリジン)

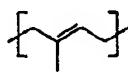
疎水性反復単位



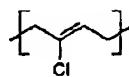
ポリブタジエン  
1, 4 - 付加物



ポリブタジエン  
1, 2 - 付加物



ポリイソプレン



ポリクロロブレン



ポリエチレン



ポリプロピレン



ポリアクリロニトリル



ポリビニルクロライド



ポリビニリデンクロライド



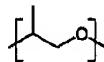
ポリビニルフルオライド



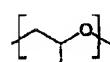
ポリビニリデン  
フルオライド



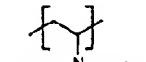
ポリヘキサフルオロ  
プロパン



ポリプロピレン  
オキサイド



ポリプロピレン  
オキサイド



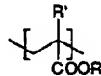
ポリ(N-ビニルカルバゾール)



ポリテトラフルオロ  
エタン



ポリシロキサン



ポリアクリレート

R = CH<sub>3</sub>, アルキルまたはアリール基

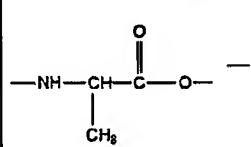
R' = CH<sub>3</sub>, すべてのアルキルまたはアリール基

R = CH<sub>3</sub>, アルキルまたはアリール基

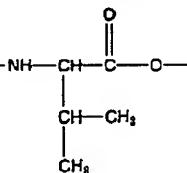
R' = CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, t-ブチル, すべてのアルキルまたはアリール基

—CH<sub>2</sub>—CH(OH)—CH<sub>2</sub> (グリシジル)

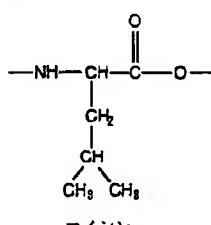
疎水性ブロックを構成するアミノ酸



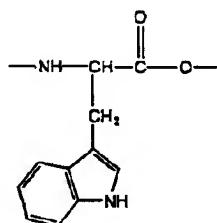
アラニン



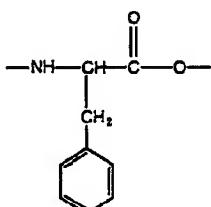
バリン



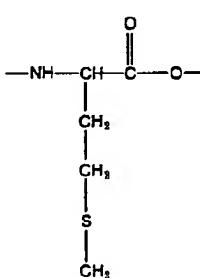
ロイシン



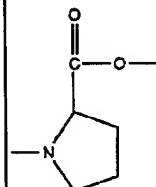
トリプトファン



フェニルアラニン



メチオニン



プロリン



























































































































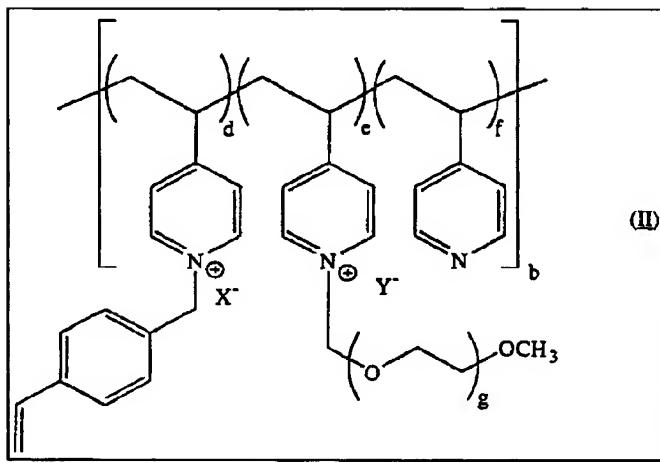


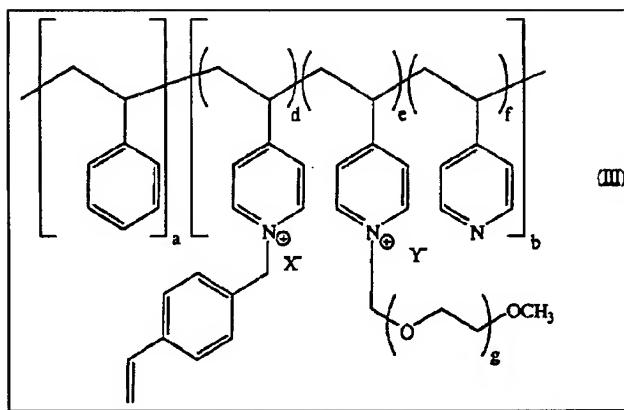


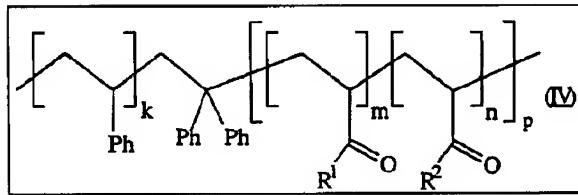


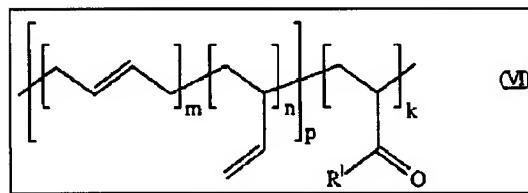
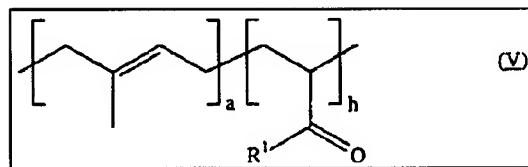












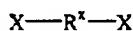
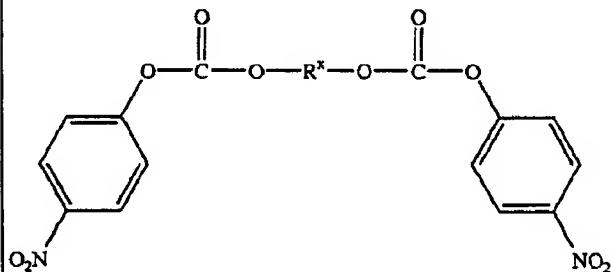
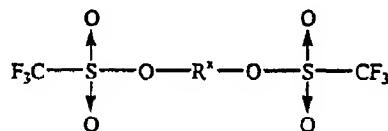
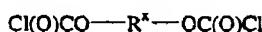
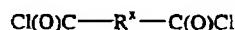
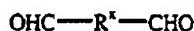
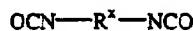
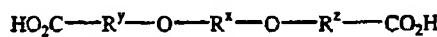
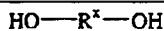
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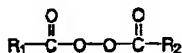
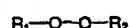






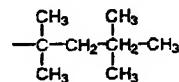
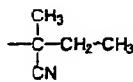
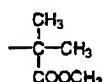
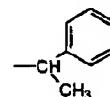
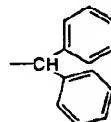
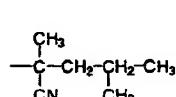
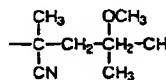
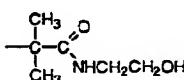
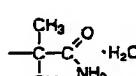
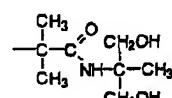
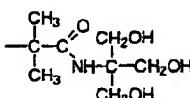
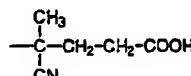
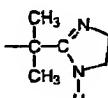
ラジカル重合の開始剤

過酸化物群



$R_1$  と  $R_2$  は以下の例を含む  
任意のアルキル基または  
アリール基であってよい。

アゾ基





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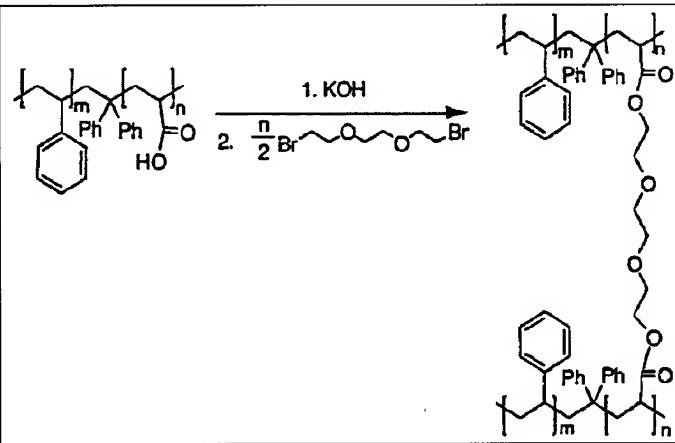
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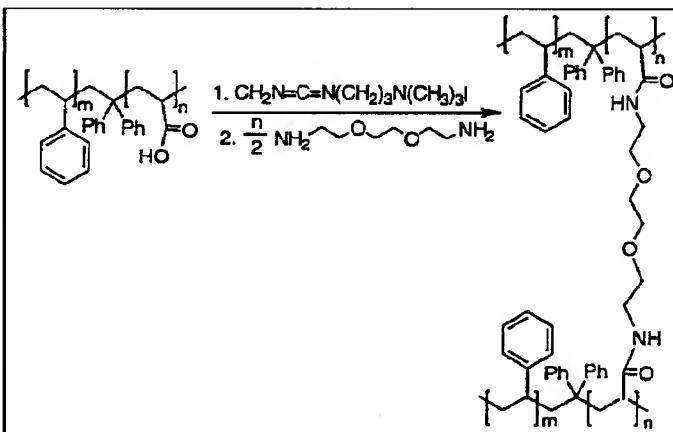


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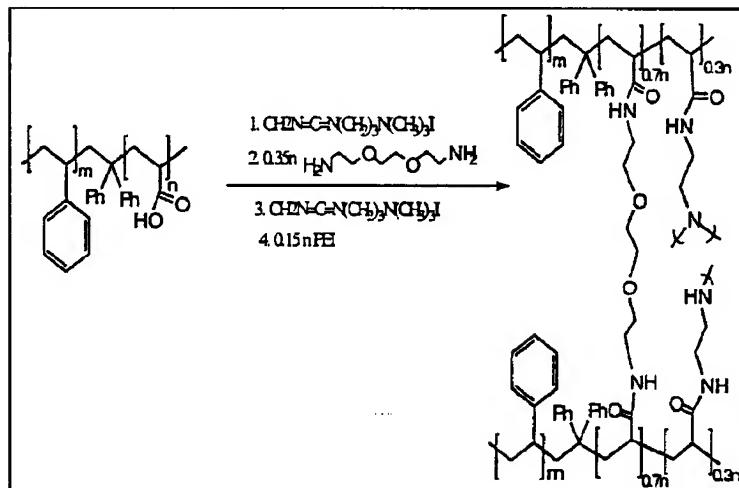
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粒子	PS:PVP 比	利マー 分子量	四級化 (%)	PEO 四級化?	ミセル 形成時間 (時間)	粒子直径 (nm)
PS:PVPブロックの長さの比における変化:						
7	1:2.0	20700	46	なし	17	9±3
8	1:1.2	14600	47	なし	12.5	15±2
9	1.9:1	14400	43	なし	19	23±4
ミセル形成時間における変化:						
10	1:2.0	20700	46	なし	2.5	7±2
7	1:2.0	20700	46	なし	17	9±3
11	1:1.2	14600	47	なし	2.5	14±2
8	1:1.2	14600	47	なし	12.5	15±2
12	1.9:1	13800	32	なし	1.75	19±4
19	1.9:1	13800	32	なし	12	27±5
四級化の百分率における変化:						
17	1:1.2	11900	15	なし	13.5	18±3
18	1:1.2	12500	21	なし	19	16±3
8	1:1.2	14600	47	なし	12.5	15±2
19	1.9:1	13800	32	なし	12	27±5
20	1.9:1	14100	38	なし	16	29±2
9	1.9:1	14400	43	なし	19	23±4
PEOの添加:						
24	1:2.0	20700 <sup>b</sup>	46 <sup>b</sup>	あり	18	12±2
7	1:2.0	20700	46	なし	17	9±3
23	1:1.2	14600 <sup>b</sup>	47 <sup>b</sup>	あり	16.5	12±2
8	1:1.2	14600	47	なし	12.5	15±2
22	1.9:1	13800 <sup>b</sup>	32 <sup>b</sup>	あり	18	22±4
19	1.9:1	13800	32	なし	12	27±5

DSC 加热 走查 No.	4		5		6		13	
	PS (T <sub>g</sub> ) C	PVP (T <sub>g</sub> ) C						
第 2	80	183	93	--	--	a	98	148
第 3	83	187	94	193	97	b	103	158
第 4	82	191	92	197	96	b	102	154
第 5	78	199	92	200	96	b	100	157

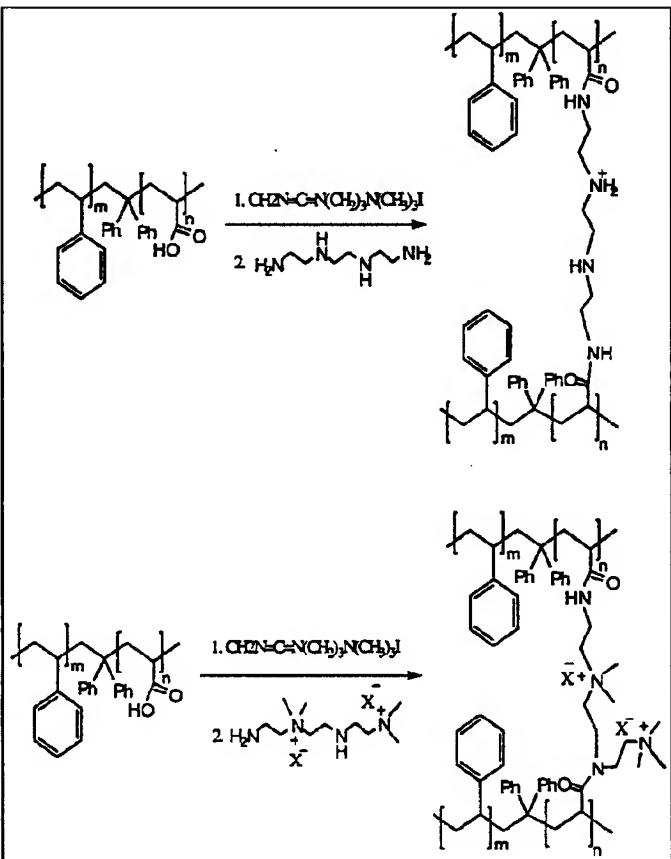


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時間	吸光度	コール酸の濃度 (mM)	コール酸の捕捉量 (g)	SCKのg当たりのコール酸のg
1分	0.520	0.200	0	0
30分	0.525	0.202	****	****
4時間	0.570	0.219	****	****
6時間	0.527	0.203	****	****
17時間	0.532	0.205	****	****
20時間	0.565	0.217	****	****

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時間	吸光度	コール酸の濃度 (mM)	コール酸の捕捉量 (g)	SCKのg当たりのコール酸のg
1分	0.36	2.0	0	0
30分	0.36	2.0	****	****
4時間	0.35	1.9	****	****
11時間	0.37	2.1	****	****
24時間	0.37	2.1	****	****

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時間	吸光度	コール酸の濃度 (mM)	コール酸の捕捉量 (g)	SCKのg 当たりのコール酸のg
1分	0.570	0.200	0	0
10分	0.590	0.207	****	****
4時間	0.557	0.189	0.09	0.009
6時間	0.525	0.184	0.54	0.054
17時間	0.521	0.183	0.63	0.063
20時間	0.511	0.179	0.99	0.099
21時間	0.522	0.183	0.63	0.063

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時間	吸光度	コール酸の濃度 (mM)	コール酸の捕捉量 (g)	SCKのg 当たりのコール酸のg
5分	0.412	1.20	0	0
45分	0.385	1.12	1.8	0.17
1時間	0.390	1.14	0	0
2時間	0.330	0.961	16.3	1.5
6時間	0.330	0.961	16.3	1.5
19時間	0.310	0.903	21.5	2.0
21時間	0.317	0.923	19.9	1.8
22時間	0.327	0.950	17.2	1.6

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時間	吸光度	コール酸の濃度(mM)	コール酸の捕捉量(g)	SCKのg当たりのコール酸のg
0分	0.391	1.205	0	0
15分	0.380	1.166	****	****
1時間	0.372	1.142	****	****
3時間	0.364	1.117	2.0	0.19
6時間	0.348	1.068	6.5	0.63
12時間	0.334	1.025	10.4	1.01
22時間	0.315	0.967	15.4	1.50
28時間	0.325	0.997	12.9	1.25
32時間	0.325	0.997	12.9	1.25

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時間	吸光度	コール酸の濃度(mM)	コール酸の捕捉量(g)	SCKのg当たりのコール酸のg
0分	0.370	1.20	0	0
30分	0.346	1.12	1.8	0.18
1時間	0.346	1.12	1.8	0.18
3時間	0.346	1.12	1.8	0.18
7時間	0.344	1.12	1.8	0.18
9時間	0.342	1.11	2.7	0.27
18時間	0.340	1.10	3.6	0.36
20時間	0.332	1.08	5.4	0.54

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時間	吸光度	コール酸の濃度 (mM)	コール酸の捕捉量 (g)	SCKのg 当たりのコール酸のg
0 分	0.406	1.20	0	0
30 分	0.382	1.13	0.90	0.10
1 時間	0.382	1.13	0.90	0.10
3 時間	0.381	1.13	0.90	0.10
7 時間	0.385	1.14	****	****
9 時間	0.374	1.10	3.6	0.40
18時間	0.366	1.08	5.4	0.60
20時間	0.356	1.05	8.1	0.90

—

時間	吸光度	コール酸の濃度 (mM)	コール酸の捕捉量 (g)	SCKのg 当たりのコール酸のg
0分	0.400	1.20	0	0
30分	0.396	1.19	****	****
1時間	0.392	1.18	****	****
3時間	0.385	1.16	****	****
7時間	0.386	1.16	****	****
9時間	0.384	1.15	****	****
18時間	0.366	1.10	3.6	0.36
20時間	0.362	1.08	5.4	0.54

—

時間	吸光度	コール酸の濃度 (mM)	コール酸の捕捉量 (g)	SCKのg 当たりのコール酸のg
0分	0.378	1.20	0	0
30分	0.363	1.15	0	0
1時間	0.354	1.12	0	0
3時間	0.382	1.21	0	0
7時間	0.368	1.17	0	0
9時間	0.366	1.16	0	0
18時間	0.365	1.16	0	0
20時間	0.367	1.17	0	0

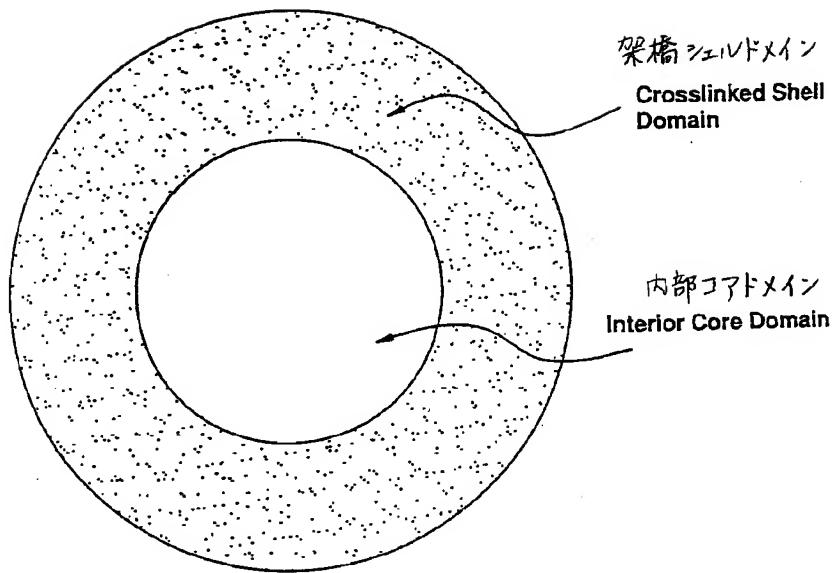


FIG.1

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 97/11345

## A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 9/51, A 61 K 9/16, A 61 K 9/107, A 61 K 47/30,  
 A 61 K 47/48

According to International Patent Classification (IPC) or to both national classification and IPC 6

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/15590 A1 (ABACOL LTD.) 21 July 1994 (21.07.94), abstract, claims 1-4, examples. --	1,2,7, 14-23
X	WO 94/17789 A1 (SHIELD RESEARCH LTD.) 18 August 1994 (18.08.94), abstract, claims 1-5, 11, examples 1-5, page 4, lines 3-26. --	1,2,7, 14-23, 32,34, 37
X	EP 0007895 A1 (COUVREUER, P. et al.) 06 February 1980 (06.02.80), abstract, claims 1,2,4,5, example 1, page 1, line 1 - page 2, line 10. --	1,15, 16,18- 26,32- 37

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

T' later document published after the international filing date or priority date and not in conflict with the application but used to understand the principle or theory underlying the invention

X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z' document member of the same patent family

Date of the actual completion of the international search  
22 October 1997

Date of mailing of the international search report

11.11.97

## Name and mailing address of the ISA

European Patent Office, P.O. Box 8000  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Fax. 31 651 epo nl  
Fax (+31-70) 340-3016

## Authorized officer

MAZZUCCO e.h.

## INTERNATIONAL SEARCH REPORT

-2-

Internat'l Application No.  
PCT/US 97/11345

## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4844900 A (ANTONIO OSUNA CARILLO DE ALBORNOZ et al.) 04 July 1989 (04.07.89), abstract, claims 1-11. --	1,15, 18-26, 32,37
A	CH 594444 A5 (BIRRENBACH, G. et al.) 13 January 1978 (13.01.78). claims I,II, column 1, lines 1-13, column 2, lines 51-68, column 6, line 50 - column 8, line 5. --	1,12, 14-16, 18-26, 29,30, 32,34, 36,37
A	US 5384333 A (DAVIS, P.A. et al.) 24 January 1995 (24.01.95), claims 1-4,10, abstract. --	1-11, 15-35, 37
A	EP 0577215 A1 (STERLING WINTHROP INC.) 05 January 1994 (05.01.94), claims 1,6,13,21,22,27. --	1-11, 15-35, 37
A	Database WPIL on Questel, week 9330, London: Derwent Publications Ltd., AN 93-236499, Class A61K; & EP,A2,0552802 (EASTMAN KODAK CO.), abstract. --	1-37
A	Database WPIL on Questel, week 9333, London: Derwent Publications Ltd., AN 93-261-669, Class C 08 F; & JP,A,5-178916 (KAO CORP.), abstract. --	1-37
A	Database WPIL on Questel, week 8925, London: Derwent Publications Ltd.. AN 89-179802, Class C 08 F; & EP,A,0320930 (WACKER CHEMIE GMBH), abstract. -----	1-37

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/11345

### Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 32-35 partially and 37 completely 1st(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(e).

### Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

